

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
PATENT DEPARTMENT
HELLER EHRMAN LLP
4350 LA JOLLA VILLAGE DRIVE
SAN DIEGO, CA 92122-1246

Received

MAR 13 2007

SD Heller

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 09 MAR 2007	
FOR FURTHER ACTION	See paragraphs 1 and 4 below
International filing date (day/month/year) 30 September 2005 (30.09.2005)	

Applicant's or agent's file reference
43177-000PC **0006 PC**
International application No.
PCT/US05/35027

Applicant
LEE, NANCY M.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer

Gary Benzion

Telephone No. (571) 272-1600

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 43177-000PC	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US05/35027	International filing date (day/month/year) 30 September 2005 (30.09.2005)	(Earliest) Priority Date (day/month/year) 30 September 2004 (30.09.2004)
Applicant LEE, NANCY M.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
- b. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I
2. ☒ Certain claims were found unsearchable (See Box No. II)
3. ☒ Unity of invention is lacking (See Box No. III)
4. With regard to the title,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
 - a. the figure of the drawings to be published with the abstract is Figure No. ____
 - ☐ as suggested by the applicant.
 - ☐ as selected by this Authority, because the applicant failed to suggest a figure.
 - ☐ as selected by this Authority, because this figure better characterizes the invention.
 - b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/35027

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material



a sequence listing



table(s) related to the sequence listing

b. format of material



on paper



in electronic form

c. time of filing/furnishing



contained in the international application as filed



filed together with the international application in electronic form



furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/35027

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12 and 13
because they relate to subject matter not required to be searched by this Authority, namely:
These claims are directed to a computer signal embodied in a transmission medium (i.e. a signal per se), which are not statutory subject matter in this Searching Authority.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-7 and 10-17
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/35027

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8): C07H 21/02 (2006.01); C12P 19/34 (2006.01); C07K 1/00 (2006.01); G01N 33/536 (2006.01)

USPC: 536/23.1; 435/91.2; 530/350; 436/536

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1; 435/91.2; 530/350; 436/536

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Medline, US Patent database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN, L. et al. Alteration of gene expression in normal-appearing colon mucosa of APCMin mice and human cancer patients. Cancer Research, May 15, 2004, volume 64, pp 3694-3700.	10, 11
Y	See entire document, especially page 3694, column 2, "Preparation of Human Colonic Mucosal Cells" and page 3695, column 1, "Extraction and Preparation of RNA" and "Analysis of Gene Expression", column 2, "Statistical Analysis" and Table 1.	1-7, 13-17
Y	BUCK, G.A. et al. Design strategies and performance of custom DNA sequencing primers. BioTechniques, September 1999, volume 27, pp 528-536.	1-7, 10, 11, 13-17
Y	FUTSCHIK, M. et al. Gene expression profiling of metastatic and nonmetastatic colorectal cancer cell lines. Genome Letters, 2002, volume 1, pp 26-34. See Table 2, second gene in the list: "SAA1"	1-7, 10, 11, 14-17
Y	Stratagene Catalog, 1988, page 39: "Gene characterization kits"	1-7, 10, 11, 14-17

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document of member of the same patent family

Date of the actual completion of the international search

09 February 2007 (09.02.2007)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Date of mailing of the international search report

09 MAR 2007

Authorized officer

Gary Benzion

Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35027

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HE, T.C. et al. Identification of c-MYC as a target of the APC pathway. Science. 1998 Sep 4;281(5382):1509-12. See abstract and figure 1: c-myc	1-7, 10, 11, 14-17
Y	KOH, T.J. et al. Gastrin is a target of the beta-catenin/TCF-4 growth signaling pathway in a model of intestinal polyposis. J Clin Invest. 2000 Aug;106(4):533-9. See Introduction: c-myc, cyclin D1, PPAR-delta	1-7, 10, 11, 14-17
Y	NOTTERMAN, D.A. et al. Transcriptional gene expression profiles of colorectal adenoma, adenocarcinoma, and normal tissue examined by oligonucleotide arrays. Cancer Res. 2001 Apr 15;61(7):3124-30. See "Relative Expression in Neoplastic and Normal Tissue" beginning on page 3125: Gro-gamma, osteopontin, c-myc	1-7, 10, 11, 14-17
X	QIAGEN News, Issue no. 5, 2002, page 21: RNAlater TissueProtect Tubes.	14
Y		15
X	US 5,837,452 A (CLARK et al) 17 November 1998 (17.11.1998), column 15, line 66 through column 16, line 19.	14, 15
Y	US 2004/0241710 A1 (GISH et al), paragraph [0061]	16, 17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35027

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-7, 10, 16-17, drawn to methods of nucleic acid analysis.

Group II, claim(s) 8-9, drawn to methods of protein analysis.

Group III, claim(s) 11, drawn to computer-readable media.

Group IV, claim(s) 14-15, drawn to kits for detection of colorectal cancer.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: at least claim 14 of Group IV is anticipated by Qiagen News, Issue No. 5, published 2002. This publication discloses a kit called RNAlater TissueProtect Tubes (catalog number 76154, top of page 21). This kit contains collection tubes containing a reagent for RNA stabilization. Since this reagent is used to preserve RNA, this reagent can be used in the analysis of polynucleotide expression levels.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35027

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
PATENT DEPARTMENT
HELLER EHRMAN LLP
4350 LA JOLLA VILLAGE DRIVE
SAN DIEGO, CA 92122-1246

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 43177-000PC		Date of mailing (day/month/year) 09 MAR 2007 FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/US05/35027	International filing date (day/month/year) 30 September 2005 (30.09.2005)	Priority date (day/month/year) 30 September 2004 (30.09.2004)
International Patent Classification (IPC) or both national classification and IPC IPC (8): C07H 21/02 (2006.01); C12P 19/34 (2006.01); C07K 1/00 (2006.01); G01N 33/536 (2006.01) USPC: 536/23.1; 435/91.2; 530/350; 436/536		
Applicant LEE, NANCY M.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 11 February 2007 (11.02.2007)	Authorized officer Gary Benzion Telephone No. (571) 272-1600
---	---	--

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/35027

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☒ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☒ on paper
☒ in electronic form

c. time of filing/furnishing

- ☒ contained in the international application as filed.
☒ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/35027

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application
☒ claims Nos. 12 and 13

because:

- ☒ the said international application, or the said claim Nos. 12 and 13 relate to the following subject matter which does not require an international search (*specify*):

These claims are directed to a computer signal embodied in a transmission medium (i.e. a signal per se), which are not statutory subject matter in this Searching Authority (see PCT rule 67.1).

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☐ no international search report has been established for said claims Nos. _____

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/35027

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)
4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-7, 10, 11 and 14-17

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/35027

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Claims 1-7, 16-17 YES

Claims 10, 11, 14, 15 NO

Inventive step (IS)

Claims NONE YES

Claims 1-7, 10, 11, 14-17 NO

Industrial applicability (IA)

Claims 1-7, 10, 11, 14-17 YES

Claims NONE NO

2. Citations and explanations:

Claims 1-7 and 11 have novelty, based on the finding that these claims require the synthesis and use of either all of SEQ ID NOS: 33-64 (claims 1 and 2) or at least a plurality of pairs of primers selected from SEQ ID NOS: 33-64 (claims 3-7) or require obtaining data from all genes represented by SEQ ID NOS 1-16. Claims 16 and 17 have novelty, based on the finding that these claims require monitoring the response of at least two biomarkers selected from the group identified by SEQ ID NOS: 1-32 in connection with screening drugs.

Claim 10 lacks novelty, being anticipated by Chen et al, who teach obtaining a plurality of quantified levels of cDNA for polynucleotides selected from SEQ ID NOS: 1-16, comparing the data with control data using multivariate statistical analysis and diagnosing colorectal cancer (see Table 3, page 3699 and see "Statistical Analysis", page 3695, column 2). Chen et al teach 15 of the 16 genes corresponding to SEQ ID NOS: 1-16 (compare Table 1, page 3695 of Chen et al with Table 1, page 14 of the instant application).

Claims 14 and 15 lack novelty, being anticipated by Clark et al, who teach a kit (column 15, line 56) comprising a swab (column 16, line 1), a collection container ("tube"; column 16, line 3), and at least one reagent "used in the analysis of polynucleotide expression levels" ("permeabilization reagent"; column 16, line 3). These are all the components required by the claims.

Claims 1-7, 10, 11, and 14-17 lack inventive step. Claims 10, 14 and 15 lack inventive step for the same reasons discussed above. Claims 1-7 lack inventive step over Chen et al, Futschik et al, and Buck et al. Chen et al establish that at least 15 of the 16 genes represented by SEQ ID NOS: 1-16 were known in the prior art to have altered expression in colon cancer (see page 3695, column 1, "Analysis of Gene Expression"; "We analyzed 15 genes, all of which have previously been shown to be altered in expression in human colon cancer."). Futschik et al disclose that the one gene missing from the Chen et al reference (SAA1) was also known to have altered expression in colon cancer (see Table 2, page 30, second gene in the list). Therefore, there was obvious reason to measure expression of these 16 genes (as well as any other genes known to have altered expression) as a way of diagnosing or monitoring colon cancer. For this reason, there was motivation to make at least a pair of primers corresponding to each of these genes for the purpose of measuring the expression of those genes (e.g. by RT-PCR or by using the primer pairs to synthesize a PCR product to use as a probe on a microarray). While neither Chen et al nor Futschik et al disclose the particular primers represented by SEQ ID NOS: 33-64, Buck et al provide evidence that all primers derived from a known sequence can be considered equivalents for the purpose of detecting that sequence (Buck et al showed that multiple different primers selected from a known sequence by multiple different groups of investigators performed adequately in sequencing reactions). Furthermore, the practices of dilution, aliquoting and lyophilization (claims 1 and 2) were well known practices in nucleic acid chemistry and do not lend any patentable distinction over the references discussed. The general idea of making kits for studying nucleic acids is found in the 1988 Stratagene Catalog (page 39). The idea of computer-readable media containing instructions for statistical analysis of gene expression data (claim 11) is obvious in view of Notterman et al, who used such software (see page 3124, last paragraph "Statistical and Database Methods"). The concept of using gene expression data to screen for new drugs in colon cancer (claims 16 and 17) is obvious in view of Gish et al (paragraph [0061]).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/35027

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-7, 10, 11, and 14-17 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: while Applicants have shown their methods to be enabled for the purposes of colon cancer, there is no evidence to show that the claims are enabled for the other diseases recited in the claims, or how, for example in claim 4, sampling rectal mucosal cells would allow for the detection of Alzheimer's disease (one of the diseases recited in claim 3).

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.